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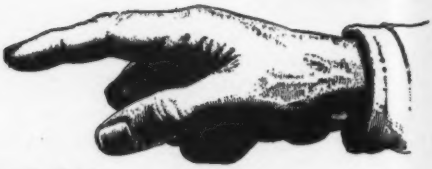
INFANTILE DIARRHEA

COLIC

GASTROINTESTINAL DISEASE



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TREATMENT OF LEUKEMIA IN CHILDREN WITH FOLIC ACID ANTAGONISTS*

Special Report No. 187

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"Unless we have something new to offer, or unless we are willing to try something new, I cannot see that ordinary routine treatment which has been suggested for leukemia is worth while. Unless we are going to try some new procedure, we uniformly send these patients home because, from an economic standpoint, and from the standpoint of the parents, it is much easier to have the agony over with in a hurry rather than attempt to prolong the life of a child by repeated transfusions." The speaker, Dr. F. J. Heck[1] of the Mayo Clinic was discussing a paper on "The Acute Leukemias". We quote him because his remarks very well summarize our lack of ability and resources to treat a child with leukemia prior to 1947 when Farber[2] and his associates reported on the use of folic acid antagonists in the treatment of leukemia in children. The changes since then in the treatment of this disease have been so rapid and kaleidoscopic as to make the presentation of certain facts regarding present day diagnostic and therapeutic methods desirable as a part of this course.

This presentation is based on the combined reports by Sullivan and associates and Rice and his group representing 85 patients treated at the Children's Hospital.

It may be surprising to learn that leukemia[3] takes more than 6,000 lives annually in the United States, many of them being in children. The death rate is said to have doubled in 25 years and is more than five times more frequent than infantile paralysis and about one and one-half as frequent as deaths from measles, whooping cough and diabetes mellitus combined and is about equal to appendicitis. Cook[4] states that the acute forms of leukemia are far more common in children than adults and that younger children are more often affected than older ones. In a series of 85 children

* From the Department of Pathology, Children's Hospital. Presented at the Post-Graduate Course, conducted by George Washington University School of Medicine, March 9, 1950.

with leukemia who were treated at this hospital, 65 or 75.6 per cent were under seven years of age at the time of onset and most were between the second and fourth years of life. The ratio of males to females was 1.6:1.

Acute leukemia is rather infrequently seen in the colored child. Sacks and Seeman[5] state that white persons are affected at a rate more than twice as great as nonwhites.

What is the cause for this increase in the incidence of leukemia? Undoubtedly the availability of improved diagnostic facilities is partly responsible for the increase, however this would seem insufficient to explain a rise of 330 per cent[5] during the period from 1900 to 1944. Dameshek and associates[6] speculate on the possible hazards to blood forming tissues in "civilized" living and mention the various chemicals which man may be exposed to in connection with medication, industry, farming, roads, the home and foods. They also suggest the role of radiation exposure in various occupations, X-ray therapy and diagnostic procedures, radioactive isotopes and the atomic bomb. The actual cause is unknown but the prevailing opinion according to Sturgis[6-7] is that the condition is neoplastic in nature. To date no child with leukemia has ever recovered from the disease.

What symptoms or findings should make the physician suspect that his patient may have leukemia? The following presenting symptoms and signs were obtained at the time of admission of 85 patients:

Bleeding manifestations	60
Pallor and asthenia	30
Enlargement of spleen or lymph nodes	27
Bone or joint pains	22
Enlargement of liver	12

When the physician makes his initial examination, the presence of leukemia is rarely suspected. The following were the initial diagnoses made in the last 21 patients included in this report.

Leukemia	4
Infectious mononucleosis	2
Tonsillitis	2
Anemia	2
Poliomyelitis	2

Blood dyscrasia, osteomyelitis, rheumatism, mumps, intracranial hemorrhage, enlarged bleeding adenoids, syphilis, lymphadenitis, acute infectious lymphocytosis each once.

The blood examinations made on admission for the first series of 65 patients gave the following results:

Red Blood Cell Count (63 cases)
Range—0.57–4.26 million

Average—2.40 million
Over 3.0 million—13 cases
White Blood Cell Count (64 cases)
Range 500 to 454,000
Under 12,000-33 cases (52%)
Subleukemic leukemias (64%)
Leukocytic leukemias (36%)
Thrombocyte Count (61 cases)
Range—5,000 to 150,000
Average—20,000
Over 50,000—8 cases

The first 64 patients with leukemia seen between 1938 and 1947 were diagnosed as follows:

Undifferentiated	34
Lymphocytic	21
Myelocytic	9

The last 21 patients with leukemia who have had more thorough diagnostic studies made, received the following diagnoses:

Lymphocytic	11
Myelocytic	10

The prolongation of the lives of these patients tends to make it possible to more accurately classify the leukemias as to type.

From the preceeding data one can state that the physician who wishes to be on the alert to recognize leukemia in a child should expect clinical information indicating that the patient would be pale and listless with the likelihood that some bleeding manifestation such as petechiae, bruising or actual hemorrhage would be noted. Enlargement of the lymph nodes, liver and/or spleen may or may not be present. Joint or bone pains along with some evidence of bleeding or increased capillary permeability should be sufficient to make him seriously consider the disease. He should become most suspicious that he is dealing with the disease in the presence of a normocytic and normochromic anemia with leukopenia with a marked reduction in granulocytic cells and thrombocytes. The latter occurs so frequently and constantly in juvenile leukemia that a trained technician will suspect the possibility of leukemia and look for abnormal leukocytes when such change is observed. Mark these findings well—the diagnosis of leukemia had best be considered when they are present:

Bleeding manifestations
Enlargement of lymph nodes, liver and/or spleen
Bone or joint pain
Fever
Leukopenia and thrombocytopenia
Presence of immature or abnormal leukocytes

Ordinarily the diagnosis can be made with considerable assurance on the basis of symptoms, clinical and hematologic observations. However, there will be a certain proportion of leukemia patients on whom one should make other examinations. These include roentgen examination of the long bones and examination of the bone marrow. Eleven out of twenty-one of our most recent patients complained of bone or joint pains which suggested the diagnoses of osteomyelitis, rheumatic fever, rheumatoid arthritis and endothelial sarcoma (Ewing). X-ray examination confirmed the presence of bone changes in practically all patients who complained of bone or joint pains—however a definite diagnosis of leukemia could not be made by the roentgenologist in any case on these observations alone. Dale[9] reported X-ray changes in the bones of 70 per cent of the 72 patients he examined. He suggests that routine X-ray examination of the knees, when indicated, should provide a valuable screening technique in investigating suspected cases of leukemia. A transverse band of diminished density in the metaphyses of long bones is mentioned by him and Silverman[10] as a common finding in leukemia. He also lists osteolysis, osteosclerosis and subperiosteal newbone formation as not infrequent findings. About half of Silverman's patients had bone pain. A persistent pain in a bone or joint which does not respond to chemotherapy, antibiotics or salicylates should make an X-ray examination of the long bones desirable and bone marrow examination imperative with the possibility of leukemia being kept in mind.

The examination of the aspirated bone marrow should give sufficient information to make a positive diagnosis in nearly 100 per cent of all cases. In our experience this examination has rarely failed to make or confirm the diagnosis. The examination is not a complicated one and can usually be made on the ward with the aid of a nurse to hold the patient and a technician to prepare the marrow smears. We have obtained marrow from the sternum, the tibia and the ilium. We find that the latter two sites are the most satisfactory for our purposes. The bone marrow in juvenile leukemia will ordinarily reveal a marked preponderance of blast forms of the lymphocytic or myelocytic series, reduction or near absence of megakarocytes with a marked increase in the leucoiderythroid ratio. Examination of the bone marrow has become a common laboratory aid in the clinical laboratory of all pediatric hospitals and in the hands of an experienced hematologist it at times enables the physician to make a diagnosis much earlier than he would if he depended on examination of the peripheral blood alone. As a part of the present day treatment of leukemia an initial bone marrow aspiration is required to establish a base line before therapy is started, subsequent examinations being made during treatment as a guide to its effectiveness. The proper procedures in establishing the diagnosis are:

History and physical examination
Examination of peripheral blood
X-ray examination of long bones
Examination of bone marrow

Your attention is called to the initial quotation indicating that the outlook for the treatment of leukemia was hopeless in 1940, whereas we can now say that although the disease continues to be incurable, we can give the parents of these leukemic children some measure of hope. On an average the duration of the lives in such patients has been more than doubled. After leukemia was recognized in the 64 patients who did not receive antifolic acid treatment the average duration of life was 1.8 months; whereas, those who received such treatment but have since died lived an average of 4.1 months. If six patients who are still alive were added to the 15 who lived an average of 4.1 months, the figure would be 4.6 months at this time.

Our figure of 4.6 months for the average duration of life after the onset of leukemia in our aminopterin treated cases is comparable with a figure of 2.7 months obtained from analysis of the data of Am-treated leukemias presented by Sacks et al—and 5.8 months which was obtained from the records of Weber et al. In Sacks' series, embracing 14 cases, only the 5 cases were used which fell into the pediatric age group and the other 9 cases were not included in the calculations because they were adults. The series of Weber et al embraced 24 cases in the pediatric age group and the results are all the more remarkable because only one patient in the series was over 8 years of age.

At the present time the treatment of leukemia in children is dependent on the use of the folic acid antagonists, cortisone and ACTH. Our experience has been obtained largely with the use of aminopterin. We have one patient who is now receiving cortisone.

Following the report of the preparation of an antagonist for pteroylglutamic acid by Seeger, Smith and Hultquist [11], Farber [2] drawing on his observations concerning the "accelerated phenomenon" in the leukemic process as seen in the marrow and viscera of children with acute leukemia treated by the injection of folic acid antagonists undertook to determine the possible effect of anti-folic acid preparations on leukemia in this age group. The results as reported by him and his associates in a group of 16 patients who were treated represent the first real advance made in the treatment of this "cataclysmic disaster of childhood" (Bethell). With aminopterin they were able to produce a clinical and hematologic remission which was induced without any doubt on the part of critical observers.

The exact mode of action of the folic acid antagonists is not known. They are known to inhibit bacterial growth under conditions which require

the presence of folic acid. It has been suggested that the anti-folic acid preparations act by inhibiting the nutritional availability of pteroylglutamic acid and similar substances. Oleson, Hutchings and Subbarow[12] have shown aminopterin to inhibit bacterial growth where the presence of folic acid is required. It would seem that the anti-folic acid preparation enters into the intercellular enzyme system which requires the presence of pteroylglutamic acid and because of its presence causes cell death. The inhibition by analogues of pteroylglutamic acid has been reversible when competitively proportional amounts of folic acid have been given up to a certain dose of folic acid antagonist, beyond which the addition of folic acid fails to reverse the effect of the inhibitor. The action of the antagonists on animals and humans is to cause a hypoplasia of the bone marrow with death of the leukemic cells. When given in sufficient dosage other effects are noted in the mucous membrane of the mouth and gastrointestinal tract (ulceration of the mucous membrane of the mouth and gastrointestinal tract being one of the first signs of toxemia from the drug). Diarrhoea often follows. The capillaries may be affected with evidence of purpura and hemorrhage. Alopecia has also been observed. During the period that the drug is used a gradual reduction in the leukocyte count is observed in those whose count is below normal. The percentage of immature cells and blast forms tends to return to normal. The bone marrow may show remarkable changes with reduction in the number of blast and immature forms and an increase in the number of megakarocytes. Along with these changes clinical improvement also takes place. There is usually evidence of an increased feeling of well being with improved appetite, gain in weight and return to near normal activity.

The usual dose of aminopterin is 1.0 mg., given daily until a satisfactory hematologic response or evidence of toxicity as shown by ulceration of the oral mucous membrane or diarrhoea is manifested. If there is evidence of toxic effect the drug is withdrawn until such symptoms or signs have disappeared. Once the desired clinical and hematologic effect has been obtained the patient is placed on a maintenance dose, the size and frequency of which is determined for each individual. This may be from 0.5–1.0 mg. given orally or intramuscularly every other day or possibly less frequently. At present we are giving the drug orally.

All patients are hospitalized at the time of their initial studies and are kept there until a satisfactory schedule can be worked out which will allow them to have an outpatient status. Daily blood counts including platelet counts are made until evidence of a remission is noted, then they may be made at intervals of every two to four days. Bone marrow examinations are made initially to determine the diagnosis and to help in establishing a base time for therapy. They are repeated at rather regular intervals for a

more definite evaluation of the effect of therapy than clinical signs and peripheral blood counts can give. The majority of children will usually obtain some benefit from aminopterin after approximately 16 days of treatment with an average of 11 milligrams of aminopterin.

A complete remission has been reported in approximately 30 per cent of all leukemic patients treated with aminopterin. Diamond[13] reports that a spontaneous remission was noted by him in 10 per cent of 300 children, either complete or partial, and the duration was slightly less than ten weeks. Infection usually preceded the remission in such cases. In our series of cases, partial or complete remissions lasted from 12 to 123 days, one child having two remissions of 57 and 47 days each. The average duration of a remission was 59.5 days. In our group of patients remissions were obtained as follows:

Complete	3 or 14.3%
Partial	10 or 47.6%
Slight or no improvement	8 or 38.1%

The criteria for a complete remission is as follows:

1. Subjective improvement
2. Objective clinical improvement
   a. Regression of lymphadenopathy and splenomegaly
   b. Loss of hemorrhagic tendency
3. Hematologic improvement
   a. Improved erythrocyte count
   b. Return of leukocyte count to normal
   c. Increase in thrombocytes
   d. Improvement of bone marrow
      1) 10 per cent or fewer immature leukocytes (pro- and blast forms)
      2) Normal number of megakaryocytes
      3) Normal leukoid—erythoid ratio

The beneficial effects of the antibiotics has been evident to every one who treats leukemia. Due to the lowered resistance of the leukemia patient, infection was usually an important factor in causing the death of most patients prior to the use of the antibiotics. Since they have been used many patients have been able to successfully combat infections which previously would have caused death.

While it has been possible to prolong the lives of some children with leukemia for as long as two years, all of those who have used aminopterin know that the drug will not cure the disease. Eventually the patient succumbs.

Necropsies were performed on 11 of the 15 patients who died. In 10 of the 15 hemorrhage was considered to be the cause of death. Cellulitis and agranulocytosis in one, myocardial failure and bone marrow aplasia were

given as the causes of death in each of three cases. Hemorrhage was a major finding in all. The liver and spleen were usually enlarged. The lymph nodes were not enlarged in four out of 11. Evidence of ulceration of the gastrointestinal tract was noted in three out of six of the patients who died of lymphocytic leukemia and in none of those with the myelocytic type. Two unusual findings were observed. Evidence of fungus or bacterial invasion of various organs, particularly the kidneys was noted in four out of 11 and cirrhosis of the liver was found in three, one being minimal. Whether or not cirrhosis of the liver could have been caused by use of the anti-folic acid drug could not be determined.

The absence of ulceration of the gastrointestinal tract in the patients with myelocytic leukemia suggests that the lymphocytes are more susceptible to the action of aminopterin and related compounds, than cells of the myelocytic series.

We feel that with the use of the folic acid antagonists the effectiveness of the treatment of juvenile leukemia has taken a distinct step forward, however some workers in this field are of the opinion that from the clinical standpoint we have not advanced very far despite the tremendous amount of work required in the treatment of this disease.

Fortunately additional help has come from other sources. The use of cortisone and ACTH give promise of being valuable therapeutic weapons which are supplementing the use of the anti-folic acid drugs. The possible relationship between the adrenal cortex and lymphatic leukemia has been suggested by a number of investigators. The beneficial effect obtained by these preparations would appear to be due to their effect on the adrenal either by direct stimulation or indirectly by stimulating the pituitary.

While it is too early to predict the ultimate effect which may be obtained from these preparations, sufficient observations have been made at various centers to come to the opinion that they favorably affect the course of lymphocytic and myelocytic leukemia and that the majority of patients obtain a clinical feeling of well being following a course of treatment lasting from 20 to 30 days. Great care must be used in their administration due to the change in the electrolyte balance and certain endocrine disturbances. Sodium retention and potassium deficiency may be expected. Cushing's syndrome is often noted.

Readjustment of the hematological values of the peripheral blood and bone marrow are said to take place in most cases. One of the most satisfying benefits obtained from the use of cortisone or ACTH is the effect on the blood vessels. Capillary hemorrhage tends to cease after four or five days of their administration. We consider this an outstanding achievement as we have been quite unsuccessful in stopping the hemorrhages seen in leukemia by giving blood transfusions, protamine or other agents. Remissions

have lasted for as long as two and one-half months and may be complete when ACTH or cortisone are used. Our experience with any of these preparations is limited to but one patient, whose case will be reported briefly as his course with aminopterin and cortisone demonstrates the possible benefits which may accrue to certain patients from the newer therapeutic aids.

This 7.5 year old white male was pefectly well until January, 1949 when a large cervical lymph node was noted which did not respond to chemotherapy. From a biopsy in April, the diagnosis of lymphosarcoma was made. Roentgen therapy failed to cause improvement. From June to September the diagnosis of rheumatic fever was also considered because of cervical adenopathy, fever, and arthralgia. Because he did not respond to salicylate therapy, a bone marrow aspiration was performed and this revealed evidence of acute leukemia, lymphocytic in type.

Aminopterin was begun on October 3. Following this he improved hematologically and clinically, aminopterin being given all the while. Late in November he was clinically free of symptoms, eating and gaining well, and maintaining a normal peripheral blood. The bone marrow at this time was essentially normal.

In mid-December, fever, polyarthritis, hempatosplenomegaly and reversal in the peripheral blood and bone marrow picture occurred. The course was downhill and by mid-February 1950, he was bed-ridden, bleeding from numerous sites, cachectic, semicomatose, and entirely refractory to a new course of aminopterin.

Cortisone acetate was begun on February 22, 1950 and one week later on March 1, his bleeding tendency had stopped, oral and skin ulcerations were healing, bone pains had disappeared, he no longer required intravenous fluids and blood, and he was out of bed, having gained twelve pounds. The bone marrow had nearly returned to normal. The cessation of bleeding at this time was very remarkable because the platelet count by the Reese-Ecker method was only 30,000 mm³ and did not rise above 50,000 mm³ until five days later.

Peripheral Hemograms

	HB	RBC	WBC	BLASTS	PRO	BAND	POLY	LYMPHS	MONO	EOSIN	PLATELETS
October	12.0	3.8	4.4	4	28	13	13	35	4		110,000
November	11.0	3.6	4.5	3		17	24	55		1	300,000
December–January	11.0	3.5	3.0	18	26	2	18	34			53,000
March	9.0	3.1	2.2		3	39	39	19			220,000

Bone Marrow Examinations

	E:L	MEGAKARYOCYTES	PER CENT IMMATURE CELLS	INTERPRETATION
October	1:90	almost absent	90–100%	Acute leukemia
November	1:2	abundant	2%	Nearly normal marrow
December–January	1:116	reduced	25%	Nearly replaced by lymphoid series
March	1:3	reduced	7%	Nearly normal marrow

At the present time we still consider aminopterin the first preparation of choice, because of its availability, ease of administration, and the likelihood of benefit being obtained following its use. We would reserve the use of cortisone and ACTH to patients who are refractory to the folic acid analogues or to the acute fulminating case with hemorrhage. X-ray, nitrogen mustard and urethane have little use in the treatment of leukemia of children.

SUMMARY

We have reported 64 juvenile patients with leukemia who received transfusions and such other treatment as was used prior to the use of anti-folic acid drugs and 21 similar patients who were treated with aminopterin and related compounds, one now receiving cortisone acetate. The acute form of leukemia is common between the second and fourth years of life. Males are affected more often than females. The cause of leukemia is unknown but it is considered by many to be a malignancy affecting the blood forming organs. The most common findings in leukemia are bleeding manifestations, enlargement of the liver, spleen or lymph nodes, bone and joint pains, fever, leukopenia and thrombocytopenia with the presence of immature or abnormal leukocytes in the peripheral blood. The disease is frequently confused with rheumatic fever, osteomyelitis and endothelial sarcoma.

Bone changes as recognized by X-ray may aid in making the diagnosis. Bone marrow examination will usually make the diagnosis. Patients treated with the anti-folic acid drugs and the antibiotics have lived over twice as long as those treated with transfusion alone. Aminopterin and related compounds will cause a complete remission lasting two months or more in approximately 15 per cent of patients, partial remission in 50 per cent. About 35 per cent will obtain little benefit. Death usually is due to hemorrhage. Infection may be a major factor, however the use of the antibiotics has unquestionably prolonged the lives of many patients. The use of cortisone acetate and ACTH have added new weapons in the treatment of juvenile leukemia which give promise of considerable benefit. The folic acid antagonists remain the drugs of choice at present, reserving cortisone and ACTH for the acute fulminating type of leukemia with hemorrhage or to the patient who has become refractory to the anti-folic acid drugs.

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A SUGGESTED CLASSIFICATION OF JAUNDICE IN INFANTS AND CHILDREN

Robert O. Warthen, M.D.

Jaundice is generally classified as retentive and obstructive. The purpose of this paper is to emphasize the partial obstructive phase and to utilize three phases of jaundice in developing a suggested classification; namely, retentive (hepatic, hemolytic), partial obstructive, and complete obstructive. All cases of jaundice will fall under one of these three phases, many exhibiting more than one phase over a period of time. Retentive jaundice may be hepatic or hemolytic in character, hepatic denoting all forms of liver damage and hemolytic constituting destruction of red blood cells. Partial obstructive jaundice refers to partial occlusion, either extrinsic or intrinsic, of any portion of the biliary duct system. Complete obstructive jaundice refers to complete occlusion, usually intrinsic, of the biliary duct system.

The three phases are most accurately diagnosed through daily qualitative stool and urine urobilinogen and bilirubin determinations. The daily evaluation of such data is of utmost importance in establishing a shift from one phase to another. Liver function tests are of value mainly in determining the presence or absence of hepatic cellular damage; they are of negligible value in establishing phases of jaundice. Qualitative van den bergh determinations are too often misleading and inaccurate to offer any substantial aid. Quantitative van den berghs and icterus indices are of value in establishing the degree of jaundice.

SUGGESTED CLASSIFICATION OF JAUNDICE IN INFANTS AND CHILDREN

I. *Retentive* (*hepatic, hemolytic*) jaundice
   a. Hepatic—liver damage present.
   b. Hemolytic—may be associated with liver damage.
II. *Retentive* (*hepatic*) jaundice with superimposed transient *complete obstructive* jaundice, followed by *retentive* (*hepatic*) jaundice which may or may not persist.
III. *Partial obstructive* jaundice with or without liver damage.
IV. *Partial obstructive* jaundice alternating with *complete obstructive* jaundice with or without liver damage.
V. *Complete obstructive* jaundice with or without liver damage.

An elucidation of this classification follows: Preceding the lists of disease entities comprising the five classified groups are comparisons of the laboratory data from classical textbook cases with representative cases from our files. In order to correctly interpret the laboratory results obtained, one

must rely on the overall day to day picture, for occasional misleading data are not infrequently encountered.

CLASSIFICATION

I *Retentive (hepatic hemolytic)* jaundice (this refers to all forms of liver cell damage with jaundice and hemolytic jaundice which may or may not be associated with liver damage).

	STOOL		URINE		LIVER FUNCTION TESTS
	UROBILINOGEN	BILIRUBIN	UROBILINOGEN	BILIRUBIN	
Classical Case	+ to increase	+ to increase	+ to increase	Variable	Van den bergh-ind. or biphasic up to 15 mgm. % bilirubin A. Hepatic-abnormal B. Hemolytic—may be abn. Icterus Index: 15-300 U.
Portal cirrhosis R.A. 41-4644 (hepatic)	Not done	16 + 1 trace 5 −	22 + 2 −	26+ 2−	Ceph. Flocc. 4+(48 hr.) Prothr. time 22-80% normal Cholesterol 100 mgm% Platelets 50,000/cu.mm. Sedimentation rate 22-48 Others negative

A. Hepatic
1. Benign or malignant neoplasm of the liver
   Carcinoma
   Sarcoma
   Lymphoma
   Adenoma
   Hemangioma
   Echinococcus cysts (hydatid cysts)—50% eosinophilia, positive intradermal skin test of Casoni with sterile hydatid fluid, positive precipitin and complement fixation tests
   Fibroma
   Endothelioma
   Teratoma
   Hamartoma
   Hepatoma
2. Syphilitic hepatitis (syphilitic cirrhosis, congenital syphilis)
   Positive Wassermann and Kahn in maternal and occasionally in infant blood.
   Positive Wassermann and Kahn in infant's cerebrospinal fluid
   Positive x-ray studies of infant's long bones
3. Portal (Laennec's) cirrhosis

4. Hemochromatosis
5. Hanot's biliary cirrhosis (non-obstructive in origin)
6. Inflammatory mass within the liver
   Abscess—due to pyelophlebitis or omphalitis with suppurative phlebitis of umbilical vein
   Gumma
   Tubercle
   Hodgkin's
7. Banti's disease
8. Hepatolenticular degeneration (Wilson's disease)
9. Juvenile cirrhosis

B. Hemolytic
1. Erythroblastosis foetalis (icterus gravis neonatorum)
   Progressive macrocytic anemia—hemoglobin less than 10–12 gms., red blood cells less than 3.0 million
   Erythroblastemia (very immature erythrocytes) of over 10% of the white blood cell differential or under 10% in prematures
   Low platelet count
   Prolonged bleeding and coagulation time for first few days of life
   Polychromatophilia, occasional stippling
   Color index high
   Rh phenomenon—Rh antibody titer is high in maternal blood
   Reticulocytes increased.
2. Septic jaundice (sepsis neonatorum, septic icterus, icterus septicemia, hemolytic septicemia)
   Anemia
   Increase in immature red blood cells (normoblasts or acidophilic erythroblasts)
   Leukocytosis
   Blood cultures may be positive
3. Physiological jaundice (icterus neonatorum, icterus simplex)
   Red blood cells (5.5–7.0 million/cu.mm.) and hemoglobin increased above normal
   Increase in immature red blood cells (normoblasts or acidophilic erythroblasts)
   Hyperchromic anemia later, poikilocytosis
   High color index
   Reticulocytes increased
   Bleeding time and coagulation time increased
   Prothrombin level low
4. Congenital hemolytic icterus (congenital acholuric jaundice, acute hemolytic anemia with jaundice, familial hemolytic icterus, familial acholuric jaundice) Uncomplicated (without stones)
   Increased fragility of red blood cells (decreased resistance to hypotonic saline solution)
   Anemia, microcytic
   Reticulated red blood cells increased
   Color index high
5. Hemolytic ictero-anemia

6. Mediterranean anemia
7. Paroxysmal hemoglobinuria
8. Mismatched transfusion
9. Sulfonamide reaction
10. Favism
11. Malaria
12. Pernicious anemia (macrocytic-hyperchromic anemia)
13. Winckel's disease—free hemoglobin in the urine
14. Buhl's disease
15. Chronic passive congestion (congestive heart failure, pulmonary disease, thrombophlebitis of inferior vena cava, congenital heart disease, etc.)
16. Sickle cell anemia (uncomplicated)
17. Jaundice and anemia of the premature
    Increase in immature red blood cells (normoblasts or acidophilic erythroblasts)
    Anemia
18. Birth trauma with cerebral hemorrhage or subdural hematoma (from which blood pigment is absorbed)
    Increase in immature red blood cells (normoblasts or acidophilic erythroblasts)
19. Snake venom

II. *Retentive (hepatic)* jaundice with a superimposed transient *complete obstructive* phase followed by a *retentive (hepatic)* phase which may or may not persist.

Early Retentive Phase

	STOOL		URINE		LIVER FUNCTION TESTS
	Urobilinogen	Bilirubin	Urobilinogen	Bilirubin	
Classical	+ to incr.	+ to incr.	+ to incr.	Variable	Van den bergh. IND. or Biphasic. Abnormal
Hepatitis M.E.N. 44–1125	This phase occurred prior to hospitalization.				

Mid-Complete Obstructive Phase

	STOOL		URINE		LIVER FUNCTION TESTS
	Urobilinogen	Bilirubin	Urobilinogen	Bilirubin	
Classical	−	− to trace	−	+ to incr.	Abnormal. Van den bergh, Immed. & Direct
Hepatitis M.E.N. 44–1125 1–12 hosp. days		1 −		2 +	None Performed

Late Retentive Phase

	STOOL		URINE		LIVER FUNCTION TESTS
	Urobilinogen	Bilirubin	Urobilinogen	Bilirubin	
Classical	+ to incr.	+ to incr.	+ to incr.	variable	Van den bergh-Ind. or biphasic Abnormal
Hepatitis M.E.N. 44-1125 (13–15 hosp. days)			2+	1+	None performed

1. Infectious hepatitis (acute simple catarrhal jaundice, catarrhal jaundice, acute catarrhal jaundice in childhood, homologous serum jaundice).
   Leukocytosis
   Anemia occasionally
   Increased resistance to red blood cells occasionally
   Plasma vitamin A levels diminished
   Wassermann and Kahn may be falsely positive
2. Acute yellow atrophy (necrosis) of the liver.
   Etiology:

Chloroform	Phenylhydrazine
Carbontetrachloride	Furfural
Avertin	Tar
Iodoform	Trinitrotoluene
Arsenic	Bismuth
Gold	Cinchophen
Phosphorus	Mushrooms
Nitrobenzene	Kala-azar
Tetrachlorethane	Bacterial toxins
Trichlorethane	Idiopathic

   Weil's disease (leptospira icterohemorrhagica, spirochaetosis)
   Spirochete in urine, blood and spinal fluid
   Positive specific agglutinin and precipitin reactions
   Positive complement fixation test
   Red Blood cells in the urine
   Albuminuria
   Guinea pig inoculation
   Yellow fever

III. *Partial obstructive* jaundice, with or without liver damage (this refers to partial obstructive jaundice which may or may not be followed by liver damage). It is to be noted that long-standing, unrelieved partial obstructive jaundice may be accompanied by secondary liver damage with a resultant superimposed retentive (hepatic) phase as evidenced by urobilinogenuria. Fortunately, jaundice usually prompts immediate medical consultation and this late phase is very rarely encountered.

	STOOL		URINE		LIVER FUNCTION TESTS
	Urobilinogen	Bilirubin	Urobilinogen	Bilirubin	
Classical	+ to decrease	+ to decrease	−	− to trace	Van den bergh-Dir.-Biphasic Abnormal to normal
Biliary duct obstruction due to extrinsic abscess JAB 46-205 (2 mos. hospitaliz.)	1 +	1 trace	1 −	1 −	Normal

1. Congenital stenosis of the bile duct
2. Benign or malignant neoplasms extrinsic to the liver (of pancreas, bile ducts, etc.)
   - Carcinoma
   - Sarcoma
   - Lymphoma
   - Adenoma
   - Fibroma
   - Endothelioma
   - Teratoma
   - Hemartoma
3. Inflammatory mass extrinsic to the liver
   - Lymph nodes
   - Abscess—adjacent to bile ducts (postoperative or otherwise)
   - Tubercle
   - Hodgkin's
   - Post-operative stricture of bile ducts
4. Peritoneal adhesions
5. Aneurysm of the hepatic artery
6. Chronic cholangitis

IV. *Paitial obstructive* jaundice alternating with *complete obstruction* with or without liver damage (this refers to cases of jaundice alternating between partial obstructive and complete obstructive phases). If the obstruction is not relieved, liver damage will result.

An alternating picture of:
Partial Obstruction

	STOOL		URINE		LIVER FUNCTION TESTS
	Urobilinogen	Bilirubin	Urobilinogen	Bilirubin	
Classical	+ to decrease	+ to decrease	−	− to trace	Abnormal or normal. Van den-bergh-Dir.-Biphasic
No example in files					

and

Complete Obstruction

	STOOL		URINE		LIVER FUNCTION TESTS
	UROBILINOGEN	BILIRUBIN	UROBILINOGEN	BILIRUBIN	
Classical	−	− to trace	−	+ to increase	Abnormal to normal Van den bergh-Immed.-Dir
No example in files					

1. Inspissated bile in the biliary tree
2. Choledochus cyst (cystic dilatation of the common bile duct, idiopathic cyst of the common bile duct)
3. Calculi in the bile ducts
   a. Pancreatic
   b. Cholelithiasis
   c. Sickle cell anemia COMPLICATED with calculi
   d. Congenital hemolytic anemia COMPLICATED with calculi
4. Parasites in the bile ducts (fasciole hepatica, ascaris, etc.)

V. *Complete obstructive* jaundice with or without liver damage (this refers to complete obstructive jaundice which, if unrelieved will be complicated by liver damage).

	STOOL		URINE		LIVER FUNCTION TESTS
	Urobilinogen	Bilirubin	Urobilinogen	Bilirubin	
Classical	−	− to trace	−	+ to incr.	Abnormal or normal. Van der bergh-Immed. & Dir.
Atresia Bile Ducts FH 47-8884 (3 wks. hospitaliz.)	5−	5− 4 trace 5+	2− 1 trace	1+ 4 trace	Cephalin flocculation 4 + (48 hrs.) others normal

1. Congenital atresia of the bile ducts (bleeding time prolonged).
2. Biliary cirrhosis, true (due to *complete* bile duct obstruction).

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SUBDIAPHRAGMATIC ABSCESS IN CHILDREN

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Case # 49-9035

A. L. M., a two year old white male was admitted to Children's Hospital on two occasions.

His first hospitalization occurred on July 22, 1949. The present illness began ten days prior to admission at which time the patient complained of a sore throat and vomited repeatedly. Marked anorexia, abdominal pain, and fever of 101.2 F. developed. A diagnosis of tonsillitis was made, but despite sulfadiazine, penicillin, and aureomycin therapy, a septic fever persisted with daily elevations up to 103 F. Two days before hospitalization, a generalized yellowish discoloration of the skin appeared. The color of the urine changed to a dark brown. No change in bowel habits occurred, and the color of the stools remained normal.

The patient had chicken pox at the age of one year. Routine immunizations were adequate and no previous serious illnesses had taken place. The birth, feeding, and developmental histories were normal. The possibility of recent ingestion of a poisonous agent was denied.

The mother had hypothyroidism which was being treated at the time of writing. The child had been exposed to a paternal aunt who was known to have active pulmonary tuberculosis.

The physical examination revealed a temperature of 104 F., a pulse rate of 110, and a respiratory rate of 20. The patient was a well developed and nourished white male with a definite pale yellow tinge to the skin. The sclerae were clear. The only other positive, abnormal physical finding was the presence of an hepatomegaly. The liver edge was palpated 6.0 centimeters below the right costal margin. It was smooth, firm, and non-tender.

An intensive laboratory investigation followed:

1. The hemogram revealed a mild anemia; the hemoglobin was 9.5 grams, and the erythrocytes numbered 3.0 million per cubic millimeter. The leukocytes varied between 10,000 and 14,000 per cubic millimeter with normal differential counts.
2. Repeated urinalyses were within normal limits. Bilirubin, urobilinogen, and urobilin were absent.
3. Tests of liver function were normal. The icteric index was 4.0 units and the cephalin flocculation test was negative at 24 and 48 hours.
4. The serological tests for syphilis were negative.
5. Repeated blood cultures failed to grow out any pathogenic organisms.
6. No cold agglutinins were demonstrable in the blood.
7. Stool cultures were negative for pathogens, ova, and parasites.

8. No agglutination of the patient's blood was present with typhoid, paratyphoid, and brucella antigens.

9. The Paul-Bunnell test for heterophile antibodies was normal.

10. A series of intracutaneous tests for tuberculosis and histoplasmosis were negative.

11. An X-ray of the chest revealed "the right diaphragm to be elevated". An increased radiodensity was noted over the right chest with a compensatory emphysema on the left side. An intravenous pyelogram did not reveal any abnormality.

At no time during this first hospital stay did the child appear toxic or acutely ill. Twenty-four hours after admission the "icterus" had disappeared. For the first six days, the treatment was entirely symptomatic and supportive. A whole blood transfusion of 250 cubic centimeters was administered on the second day. During this interval an intermittent fever was present ranging between 101 F. and 103.8 F. Aspirin was given for fever. On the sixth day, therapy with chloramphenicol was instituted. The dosage was 250 milligrams every three hours. Within seventy-two hours, the temperature was normal and remained so for the duration of hospitalization. The hepatomegaly persisted, however. The patient was discharged 17 days after admission with a diagnosis of atypical virus pneumonia accompanied by a mild hepatitis.

Eight days after discharge, the child was readmitted to the hospital. The interim history revealed a recurrence of fever and anorexia. In addition several "tarry" stools had been passed.

Physical examination at this time showed a temperature of 102 F., pulse 100, and respiratory rate 30. Marked tonsillitis and cervical adenitis were the only abnormalities noted.

A urinalysis was normal. The hemogram showed 11.0 grams of hemoglobin, 3.8 million erythrocytes per cubic millimeter, and 22,000 leukocytes per cubic millimeter of which 69 per cent were neutrophils. An X-ray of the chest was interpreted as normal.

No specific therapy was instituted. The fever continued with a range between 98 F. and 104 F. On the third hospital day, the patient was signed out by his parents and taken to the Harriet Lane Home in Baltimore, Md.

For three weeks a septic temperature curve persisted despite therapy with sulfadiazine and aureomycin. The only significant laboratory studies during this period were four blood cultures which grew out *Staphylococcus albus*. Other procedures were essentially the same and yielded similar results as on the first admission. Roentgenogram of the chest showed an elevated right diaphragm with a small amount of fluid at the right base. On the twenty-second day, chloramphenicol and penicillin were added to the therapeutic regimen. The temperature became low-grade and a tonsillo-

adenoidectomy was performed. The pathological report on the tonsils showed numerous tubercles. All therapy was discontinued and the temperature gradually rose to 103 F. Thirty-nine days after admission, the subphrenic space was entered with a needle and a large quantity of green pus was obtained which, on culture, grew out *Staphylococcus albus*. The next day an incision and drainage of the subphrenic space was performed. Approximately 200 cubic centimeters of greenish pus were obtained. An uneventful post-operative course ensued and the child was discharged in good condition approximately three months after the onset of his illness.

DISCUSSION

From a review of the literature, it is apparent that subdiaphragmatic abscess occurs with relative infrequency in the pediatric age group. Of Gatewood's[1] 41 cases, all were adults except one who was a child aged 8 years. Brown[2] reported 4 cases under 10 years of age and one of these was only 22 months old. Ireland[3] gave a detailed discussion of 6 cases occurring in childhood. The ages ranged between 14 months and 12 years. In the cases, both collected and personal, presented by Oschner and DeBakey[4], none of the patients were younger than 9 years. Anspach[5] reported the roentgen findings in 10 children with subphrenic abscess. The largest series in children was recorded by Ladd and Swan[6] who described the condition in 14 patients under 11 years of age, 6 of whom were less than 2 years of age.

The pathogenesis of subdiaphragmatic abscess in children is varied as it is in adults (Table 1). All observers agree that a suppurative appendix is the commonest preceding event. In 15,000 collected cases[4] of acute appendicitis, approximately 0.9 per cent suffered this complication. Of 860 children[6] with acute appendicitis, 0.3 per cent developed subphrenic abscess. Thus, in the pediatric age group, subdiaphragmatic abscess as a complication of acute appendicitis appears to occur with less frequency than in adults. Whether the intra-abdominal infection is spread by direct extension up the right gutter or by way of the regional lymphatics is a moot question. Suffice it to note that intra-abdominal sepsis is the commonest precursor to localization of an abscess under the diaphragm. Although less common, blood-borne infection from a distant focus is an important source of subphrenic abscess in children. Almost one-third of the cases recorded in detail were initiated in this manner[3,6]. Intra-abdominal trauma may be an instigating factor, but occurs infrequently (one instance in the cases reviewed). It has been stated that the most common organisms present are streptococci, staphylococci, and the colon bacillus, but a summary of the reported cases reveals that there is no uniformity of organisms present. Neither racial nor sex preponderance has been demonstrated. In the majority the abscess is located on the right side.

Ladd and Swan[6] have divided the symptomatology of subdiaphragmatic abscess into three different groups which roughly parallel the modes of origin of the infection.

Group 1: The subphrenic abscess complicates the course of an acute ruptured appendicitis. This type is the one most frequently encountered. Following laparotomy, the persistence of the evidences of infection as demonstrated by continued fever, tachycardia, malaise, and leukocytosis which is unexplained by the abdominal, rectal, or urinary findings or by the condition of the wound, suggests the walling off of the infectious process in some other area. Localizing signs include tenderness along the course of

TABLE 1

Pathogenesis of Subdiaphragmatic Abscess in 21 Cases Occurring in Children

PATHOGENESIS	NUMBER OF CASES	
I. Following intra-abdominal infection		14
A. Ruptured appendix	5	
B. Acute appendicitis	4	
C. Liver abscess	2	
D. Primary peritonitis	1	
E. Chronic gastric ulcer	1	
F. Rupture of the ileum	1	
II. Metastatic from distant focus		6
A. Upper respiratory infection	3	
B. Otitis media	1	
C. Hordeola	1	
D. Lobar pneumonia	1	
III. Traumatic		1
Total		21

the twelfth rib or over the liver. Spasm in the right upper quadrant or even a palpable mass is frequently present. Pleural effusion, as suggested by dullness or flatness to percussion, diminution in tactile fremitus, and distant breath sounds, is usually found.

Group 2: Those cases in which the subphrenic infection is merely part of a widespread intra-abdominal suppurative process. In these patients there is a rather abrupt onset of what appears to be a severe infectious disease. The constitutional signs of fever, anorexia, prostration, malaise, and tachycardia are associated with some evidence of intra-abdominal involvement, e.g., vomiting, abdominal pain, diarrhea, tenderness, spasm, and decreased or absent borborygmus. The course of the disease tends to be fulminating, the patient dying within a few days from the onset.

Group 3: Those cases in which the subphrenic abscess is metastatic and is at once the chief or only disease present and the cause of the patient's

admission to the hospital. This group is, perhaps, the most difficult to diagnose. There is a history of upper respiratory infection, otitis media, or recurrent superficial staphylococcal infection. Some days later, there follows the vague and insidious onset of mild malaise and anorexia associated with low-grade pyrexia. These symptoms persist, and there begin occasional attacks of abdominal pain. These rather mild symptoms gradually increase over a period of one to three months until the patient is finally brought to the hospital because of the appearance of a mass in the upper abdomen which may be localized on the side of the disease. Usually some weight loss and mild secondary anemia are present. Examination reveals a degree or two of fever, tachycardia, leukocytosis, and a diffuse, slightly tender mass in either the right or left upper quadrant, just under the costal margin.

Roentgenographic examination may be of aid in the diagnosis, but no observable abnormality may be present, and no common variation from normal is pathognomonic. Anspach's monograph is a classic in its description of the roentgen signs of subphrenic abscess. In summary:

1. The first sign is fixation or limitation of motion of one leaf of the diaphragm. The leaf on the affected side is usually elevated. The fixation and elevation are especially noticeable at the end of deep inspiration because of a depressed leaf on the unaffected side.

2. The next sign, the first pulmonary sign, is a fuzziness of the upper surface of the diaphragm on the affected side.

3. Later, there is a slow, gradual accumulation of exudate which, early partially, and later completely, obliterates the base of the lung field and frequently presents a fairly well-defined horizontal upper margin as time goes on.

4. Occasionally, an irregular semi-transparent shadow is seen which outlines a portion of a fissure. This occurs as the exudate tends to separate the surfaces of the pleurae.

5. In extremely far-advanced or long-standing progressive cases, the pleural exudate may finally become large in amount and the lung field obliterated to a high degree, but even here there is a noticeable tendency for the basal shadow to maintain a horizontal upper margin in the absence of pneumothorax, and an almost normal relationship at the base.

6. Often an overexposed film will show evidence of air in the lower lobe otherwise obscured by the fluid and reveal the base of the lung contacting the diaphragm as normally, or it may reveal the dense, triangular shadow caused by the collapsed lower lobe.

Early and adequate drainage is the correct treatment for subdiaphragmatic abscess. Three general types of operation have been devised to solve the difficulties presented by an abscess in as relatively an inaccessible location as is the subphrenic space. These can be classified as transperitoneal,

transpleural, and extraserous, according to the route used to approach the abscess. Ladd and Swan[6] categorically state that in the light of overwhelming statistical evidence, it appears that there is no longer any justifiable reason for using any approach other than the extraserous. The other routes are attended by complications such as empyema and exacerbation of peritoneal infection, and by a rather high mortality rate. Untreated subdiaphragmatic abscess carries a mortality of from 90 to 100 per cent. With early incision and drainage plus the addition of effective antibiotic therapy, the outcome is favorable with practically no mortalities.

SUMMARY

1. A diagnostic problem finally diagnosed as a subdiaphragmatic abscess occurring in a two year old white male has been presented.
2. A review of subdiaphragmatic abscess in childhood has been attempted.

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CONGENITAL RHABDOMYOMA OF THE HEART*

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E. Clarence Rice, M.D.

R. B. 47-8433

A case of congenital rhabdomyoma of the heart is in itself somewhat of a rarity since only sixty-nine cases have been reported in the available literature as of January 1950[1]. However, when it is the first case of its kind at a specific institution it is well to review the literature for one's own benefit. Particularly interesting reviews in the American literature were written by Farber[2], Batchelor and Maun[3], Lebate[4], and Wolbach[5].

CASE REPORT

The infant, a thirteen day old white female, was admitted to The Children's Hospital on August 15 at 2:00 P.M. and died on August 16 at 6:00 A.M. She was the youngest of three siblings and the product of a nine months' gestation. The hospital delivery was normal. The family history was non-contributory. The birth weight was eight pounds, ten and one-half ounces, and the infant was considered normal. Feedings consisted of breast milk and complementary formula until the day before admission. At this time the mother noted that a bluish-white color had replaced the baby's usual red complexion and that the hands and feet were cold. Vomiting had also begun.

On admission, the above observations were confirmed and in addition paleness and circumoral cyanosis were noted. The infant, although well developed and nourished, was immediately placed in an oxygen tent. The lungs were clear and the respirations were labored and rapid. The heart was enlarged and the rate was fast. The liver was palpably enlarged and the remainder of the physical examination was non-contributory.

A chest x-ray disclosed congestion of the lungs and enlargement of the liver. The cardiac shadow was greatly enlarged to the left and the impression was congenital heart disease.

An electrocardiogram was reported as follows: auricular tachycardia with a rate of 260; the P wave could not be identified in any of the leads; the Q.R.S. complexes were widened, slurred, and inverted in all leads; the Q.R.S. interval was 0.12 seconds; the T waves were upright in all leads. The interpretation was auricular tachycardia with aberrant ventricular responses or ventricular tachycardia.

Seven hours after admission the carbon dioxide combining power of the blood was 32 volumes per one hundred milliliters, so one-sixth molar lactate

* From the Department of Pathology.

solution was begun by clysis. Nine hours after admission the respirations had increased to 90 per minute and remained unchanged until death, which occurred suddenly sixteen hours after admission.

Permission for necropsy was limited to the thorax and abdomen. The body was that of a well developed and nourished white female weighing 3.98 kilograms. The findings of importance and interest were limited to the heart and will be described. In addition to the cardiac changes, pulmonary edema and congestion, hepatomegaly with passive congestion, and passive congestion of the spleen were noted.

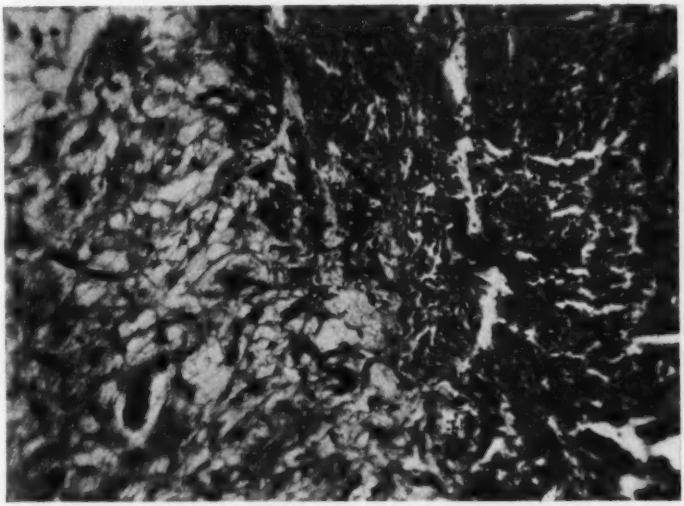

FIG. 1. Photomicrograph showing rather sharp demarcation of tumor from heart muscle. Note the vacuole-like spaces characteristic of the condition. (× 100.)

The pericardial sac was normal. The heart was very large, lay transversely in the chest and measured 7.0 centimeters in width by 4.5 centimeters in length.

The ductus arteriosus was patent and the venous return was normal. The heart weighed 53.0 grams, the normal being 19.0 grams. The valve circumferences were as follows: tricuspid—5.3 centimeters, pulmonary—2.3 centimeters, mitral—4.8 centimeters, and aortic—2.2 centimeters. The right ventricular wall averaged 0.2 centimeters in thickness and the left, 0.8 centimeters. On incising the interventricular wall, which measured 2.5 centimeters in thickness, a large encapsulated tumor mass was encountered. On cut section, it was firm, pink in color, and had several hemorrhagic

areas scattered throughout. A small domelike protrusion from the wall of the left ventricle was noted which measured 0.5 centimeters in diameter. A third tumor, measuring 1.0 x 0.7 x 0.7 centimeters was attached to the posterior edge of the mitral valve. On cut section these resembled the tumor in the interventricular septum.

On microscopic examination, some relatively normal areas of myocardium were seen; however, the fibers were small and separated from one another.

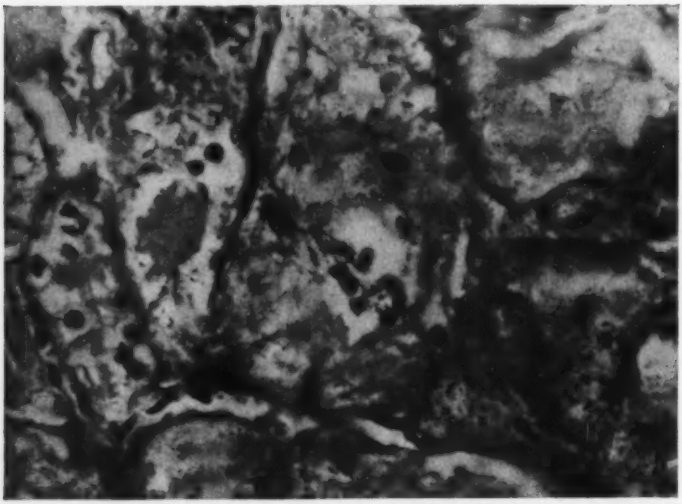

FIG. 2. High power photomicrograph showing the characteristic vacuoles which contain a finely granular translucent substance giving the typical appearance of glycogen with Best's carmine stain. The lining membrane of the vacuoles is seen as a cytoplasmic continuation from some of the cells between the vacuoles. Polymorphonuclears are scattered throughout. (× 1000.)

Sections through the tumor showed it to be fairly sharply demarcated from the "normal" myocardium.

The tumor tissue was composed of large, polyhedral branching cells with deeply stained nuclei. Three or four cytoplasmic processes sprang from the surface of each cell body to form the lining membrane of rounded, vacuolated spaces which varied in size. The branching cells had the appearance of "spider cells".

The vacuoles, stained with hematoxylin and eosin, contained a pink-staining amorphous substance within the cell wall. Best's carmine stain gave the typical appearance of glycogen. A few groups of polymorphonuclear leukocytes were seen within the vacuoles.

Sections from the tumors were examined by the Armed Forces Institute of Pathology and by Dr. Sidney Farber. Both agreed that the diagnosis was congenital rhabdomyoma of the heart.

DISCUSSION

Congenital rhabdomyoma of the heart has been discussed at length by various authors as to its origin and malignancy, and all without exception are in agreement that it is not a neoplasm. This, however, is their only point of agreement. Two other facts are worth mentioning, viz., that fifty-five per cent occur in individuals under a year of age and that the majority of the cases have been associated with congenital defects, especially of the central nervous system.

The origin of congenital rhabdomyoma has presented quite an interesting academic discussion over the years. Von Recklinghausen[6], in the first case report, considered the tumor to be composed of dilated lymph spaces. Virchow[7] was certain that the tumor was derived from hyperplasia of the myocardium; however, he conceded that the contents of the tumor might be either lymph or serous fluid. Marchand[8] in 1901 first suggested the true content of these tumors by analogy to the fetal heart and the fact that it contains glycogen. Askanazy[9] was the first to demonstrate the presence of glycogen.

The true nature of the tumor was discovered by Wolbach[5] in 1907, when, by special staining methods, he was able to point out without doubt that the elements present were representative of muscle fibre formation. This suggested to Steinbiss[10] that the tumor was perhaps derived from an embryonic cell which has retained its form, all the elements having hypertrophied. In favor of this was the reasoning that there would be more rapid growth with metastases were these true embryonic rests of usual potentiality. Rehder[11] called it a tissue malformation rather than a true tumor and applied the term hamartoma. Farber[2], in perhaps the best article of all on this subject, stated that it should be classified as one of the many deviations from the normal in growth.

Of as much importance as the origin is the association of these tumors with congenital anomalies. This suggests a congenital rather than a neoplastic origin for the condition. Over fifty per cent of the tumors are associated with other anomalies, the most common being tuberous sclerosis, cysts and tumors of the kidneys, tumors of the sebaceous glands, hare lip and cleft palate, neoplasms of the brain, and congenital malformations of the pancreas, kidneys, and lungs.

It has been thought that this condition is more common than reported. Farber[2] suggested a higher incidence might be found if complete autopsies were done in mental institutions. Using this same reasoning, only eight

years earlier, Steinbiss [10] found twenty-one cases of tuberous sclerosis over a ten year period at a mental institution, six of which had congenital rhabdomyomas of the heart.

It would seem that this condition has little clinical significance other than that it is one of the causes of otherwise unexplainable cardiomegaly and it should be suspected in all cases of tuberous sclerosis. An interesting observation is that most of the patients have become cyanotic just before death. Usually no cardiac symptoms are mentioned; however, Batchelor and Maun [3] reported that tumors situated on the valve leaflets produced murmurs. In our case, a paroxysmal auricular tachycardia was produced, as evidenced by the electrocardiogram.

SUMMARY

1. A case of congenital rhabdomyoma of the heart has been reported. A total of sixty-nine cases have been published.

2. The obscurity of the origin is mentioned.

3. Of particular significance and interest is the association of tuberous sclerosis and various other congenital anomalies with this condition.

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CLINICO-PATHOLOGICAL CONFERENCE

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William M. Crowell, M.D.

R. A., an eight year old colored male, was admitted to Children's Hospital with the history of having been well until three months prior to admission. At that time his eyes became yellow. His mother noticed at night time that he had started to fall over previously familiar objects. She also noted that his clothes were tighter about his waist and his abdomen was becoming larger. During this period his urine had become brown and his stools were lighter. On admission, the above symptoms were present along with noctural dyspnea, irritability, and anorexia. The skin was yellow in color.

The past history reveals an episode of yellow discoloration to the skin eighteen months previously which cleared coincidentally with the administration of worm medicine.

Physical examination revealed a well developed and well nourished child in no acute distress who weighed 63 pounds. His face was swollen and his eyelids were edematous. The sclerae and skin were yellow. The superficial blood vessels of the chest were prominent and petechial hemorrhages were noted on the upper and lower extremities. The purpuric lesions did not blanch on pressure and ranged in size from 0.1 to 3.0 centimeters. The heart and lungs were normal. Abdominal examination revealed distension without a fluid wave. Masses were palpable in the region of the liver and spleen, the right-sided mass being palpable one finger-breadth below the costal margin and the left-sided mass being palpable three finger-breadths below the costal margin. The left-sided mass was soft to palpation. The right-sided mass moved with respirations.

Admission laboratory work disclosed a rather severe anemia and a normal urine except for the presence of bile and urobilin. The hospital course was afebrile and transfusions were given to combat anemia and recurrent bouts of hemoptysis and/or hematemesis. During the twenty-one day preoperative period, first and second strength tuberculin tests were negative.

An exploratory laparotomy was performed on the twenty-second day.

Other laboratory data are listed below:

Blood:	Hemoglobin	8.5 grams
	Erythrocytes	2.75 million (no spherocytes)
	Leukocytes	3.5 thousand
	Neutrophiles	72 per cent

Lymphocytes	26 per cent
Monocytes	2 per cent
Bleeding time	34–60 seconds
Coagulation time (finger)	3.5–4.5 minutes
Reticulocytes	1 per cent
Thrombocytes	150,000
Prothrombin time	22–80 per cent
Van den Bergh	qualitative—immediate direct reaction; quantitative 3.8 milligrams.
Cephalin flocculation	4 plus
Glucose Tolerance Test (venous blood)—fasting	87 milligrams, one-half hour—160, one hour—147, two hours—137, three hours—90.
Sickling preparation	Negative
Fragility test	Normal
Kahn	Negative
Icterus Index	45–50 units
Total proteins	6.18 grams
Chlorides	379 milligrams
Sedimentation rate	44 millimeters (corrected)

Urine: positive for bile and urobilin; negative for galactose; few to many leukocytes.

Stools: positive for bile; negative for ova and parasites.

X-rays: chest film, abdominal flat plate and intravenous pyelogram revealed only enlargement of the liver and spleen.

DISCUSSION

Preston A. McLendon, M.D.: The history given would indicate an insidious development of jaundice as well as the change in the size of the abdomen which was apparently caused by a markedly enlarged spleen and a moderately enlarged liver. At the time of admission, the spleen was said to be rather soft which would suggest a more recent enlargement as contrasted with the firm liver which was noted. Purpuric lesions are not uncommon in liver disease. The enlargement of the superficial blood vessels of the chest and the "puffiness" or edema of the face would indicate some obstruction to portal circulation. The heart was found to be normal. The abnormal findings in the laboratory reports are: irregular prothrombin time, increased flocculation rate, and increased sedimentation rate. The latter two, in the absence of infection, would signify some liver pathology with changes in the globulin fraction. The Van den Bergh reaction and the presence of bile in the urine and stools would indicate intrinsic liver damage rather than biliary obstruction.

These findings add up to initial liver pathology with subsequent portal and splenic vein stasis resulting in the clinical picture of Banti's syndrome or as more recently designated, congestive splenomegaly.

It is interesting to speculate about the previous history of jaundice associated with the use of a vermifuge. It is possible that this child might

have been given a medication containing carbon-tetrachloride which produced a mild hepatitis with progressive pathology culminating in fatality.

PATHOLOGICAL DISCUSSION

E. Clarence Rice, M.D.: The laparotomy disclosed a liver which was of normal size, or possibly smaller, with the typical appearance of portal cirrhosis. The wall of the gall bladder was thick. There was no evidence of common duct obstruction. No biopsy was performed. Following the operation and during the remainder of his hospital stay the patient vomited blood on several occasions. Two months later he was readmitted because of hemoptysis. At this time his blood contained 3 mg. bilirubin per 100 milliliters. Nine months after the exploratory laparotomy the patient's spleen was removed. The liver was enlarged as were the mesenteric lymph nodes. No fluid was present in the peritoneal cavity. The spleen weighed 320 grams and measured 14.0 by 11.5 by 5.5 centimeters. The capsule was tense and smooth, the surface being dark purplish-red. The pulp was firm and of a homogeneous red color. The pathologist described the microscopic appearance as showing the pulp to be more compact than usual with increased connective tissue, the reticulum being prominent as compared with the lymphoid elements. Some hemorrhage had occurred. It was considered that the appearance was that of congestive splenomegaly and cirrhosis, generally regarded as Banti's disease. Immediately after the operation the serum-bilirubin increased to 8.0 mg./100 ml. and the Van den Bergh gave an immediate direct reaction. Three weeks later the bilirubin was down to 2.2 mg., and the Van den Bergh was unchanged.

The patient was again admitted to the hospital fourteen months following splenectomy, aged 10 years, because of pain in the left epigastrium and left ear. His appetite had been good and his general condition had been considered satisfactory by his parents up to the day before his hospitalization. The admitting physician found the patient to be listless and drowsy and in no acute distress. The left ear showed evidence of a perforation of the drum with some healing. The sclerae were icteric. The teeth were carious, the pharynx injected. Numerous rales were heard throughout the right chest, however there was no impaired resonance. The heart appeared to be normal. The abdomen was soft, no tenderness being elicited. The liver extended down to the umbilicus, the surface feeling firm and irregular. The temperature was 104.8 F.; pulse, 100; and respirations, 28. The admitting diagnosis was acute bronchitis, sickle cell anemia and cirrhosis of the liver. The following day he was lethargic; the pulse and respiratory rates were rapid; temperature was 103.0 F. The bleeding and coagulation times were reported as being written within normal limits; the hemoglobin was 11.0 grams per 100 milliliters; erythrocytes, 4,000,000; leukocytes, 17,000 with 80 per cent polymorphocyclears. Thrombocytes were 50,000 per cubic

millimeter. No sickling was evident. No urine was obtained and stools, which were yellow in color, were passed involuntarily. Respirations became more labored and vomiting of brown material occurred just before death, fifteen hours after admission.

The body was that of a well nourished and well developed, colored male. The skin and sclerae showed marked icterus. Abdominal scars of the two previous operations were noted.

Cisternal fluid was yellow and cloudy containing 320 leukocytes with an equal number of polymorphonuclear-leukocytes and lymphocytes. No bacteria were found on smear and culture. The brain weighed 1480 grams (normal 1270 grams). The convolutions were swollen and the pia-arachnoid was thickened adjacent to the longitudinal fissure. Section revealed a slight greenish coloration of the white matter. The ventricular system was normal. Microscopic examination verified the gross findings.

The pleural and peritoneal cavities were free of fluid and the omentum was adherent to the operative scars. All tissues showed an icteric tint. The mediastinal, bronchial, and mesenteric lymph nodes were enlarged and hemorrhagic. Microscopic examination showed an increase in reticulum with reduction of the lymphoid elements and considerable congestion.

The right and left lungs weighed 370 grams and 500 grams (normal 176 grams). The lower left lobe was firm and beefy red, the lower right showing a number of firm, red areas 1 centimeter in diameter. Microscopic examination revealed intense congestion and actual hemorrhage. The heart was somewhat enlarged, a number of small subepicardial hemorrhages being present. The myocardium was pale yellow. Microscopically the nuclei of the muscle fibers were often larger than normal—staining rather deeply. Here and there a slight accumulation of round cells was observed between the muscle fibers and bundles.

The liver weighed 1320 grams (normal 852 grams). The surface was pale, rough and nodular with a number of hemorrhagic areas. The tissue was sectioned with resistance due to increased connective tissue which enveloped nodular areas of bile-stained hepatic tissue. The extrahepatic biliary system was normal. Microscopic examination disclosed islands of polygonal cells of increased size with large, deeply staining nuclei showing some granularity of the cytoplasm. Some of the polygonal cells were bile-stained. The sinusoids contained erythrocytes and rather numerous bile capillaries and a heavy infiltration of round cells.

The stomach was markedly dilated and scattered hemorrhages were noted in the serosa of the gut. No mention is made of esophageal varices being seen. The pancreas was normal. The adrenals were congested with microscopic evidence of cortical congestion and some atrophy of the glomerular zone. The kidneys weighed 240 grams each (normal 93 grams). They

were enlarged and swollen, the surfaces being brownish-red with numerous dilated vessels. The capsule was removed without difficulty. The cut surface was edematous and congested; this fact was verified microscopically. Some small areas of calcium had been deposited in the cortex and a few of the arterioles had slightly thickened walls.

The pathological diagnosis was:

Diffuse nodular cirrhosis and subacute hepatitis,
Icterus,
Cerebral edema, and
Probable prothrombin deficiency as evidenced by:
Pulmonary hemorrhage and epicardial and intestinal serosal hemorrhages,
Renal edema with calcium deposition,
Adrenal cortical congestion with atrophy of zona glomerulosa,
Myocardial degeneration,
Peritoneal adhesions, and
Post-operative splenectomy.

In summary, we have an eight year old colored boy, who when first seen, was well developed and nourished. This child had become jaundiced when he was six years of age. The administration of a vermifuge at this time appears to be coincidental but conceivably could have some bearing on the patient's subsequent history. During the two year period he was observed by the physicians at Children's Hospital, he was always jaundiced, had evidence of hemorrhages from the esophagus or gastro-intestinal tract and into the skin. Edema was noted at times but abdominal ascites seems to have been absent throughout. Anemia was probably secondary to the continued bleeding. Evidence of parenchymal liver damage and some biliary obstruction with variable prothrombin deficiency was evident throughout the period of observation. The diagnosis of Laennac's cirrhosis with congestive splenomegaly was easily made. Splenectomy did not appear to give much benefit to the patient.

Death appears to have been due to pulmonary hemorrhage, renal edema, cardiac failure, and possibly liver insufficiency.

Whether or not this patient would have been benefited by the surgical treatment of portal decompensation other than splenectomy cannot be determined. Inasmuch as it appears that the initial pathology was probably intrahepatic, it is unlikely that operative measures would have benefitted the patient.

As to the etiology of the cirrhosis we have no definite clues. Possibly a dietary deficiency may have been a factor or the vermifuge used by the mother may have contributed to the liver damage.